mRNA Therapies in Oncology: Key Pipeline Developments and Clinical Trial Insights

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In recent years, the field of RNA therapeutics has evolved as a ground-breaking approach in medical research. Notably, the 2023 Nobel Prize in Physiology or Medicine was awarded for groundbreaking work on base modification, a critical discovery that enabled the development of COVID-19 vaccines.[1] Following this achievement, focus has now turned to leveraging RNA's intrinsic immune-activating potential for oncology, with mRNA therapies taking the lead. mRNA therapies offer unique benefits over conventional therapies like recombinant proteins and plasmid DNA, including non-integrating, cell-free production, enhanced specificity, and potency, as well as a personalized, patient-focused approach. Additionally, mRNA therapies possess ability to target undruggable targets with minimal side effects, setting them apart from conventional approaches.[2] Few mRNA therapies are entering late-stage clinical development, including, Gritstone bio's GRANITE and Moderna's personalized cancer vaccine mRNA-4157, which are leading the way and are expected to enter the market in Q2 2027 and Q3 2030 respectively, according to IQVIA Pipeline Link.

This article provides an update on current mRNA-based therapies for oncology and outlines the latest development activities, including ongoing clinical trials of key experimental drugs with data sourced from IQVIA Pipeline Link and IQVIA Trial Link.

Mechanistic basis of mRNA therapies

mRNA therapies leverage synthetic or modified mRNA transcripts to deliver tumor-associated (TAA) or tumor-specific antigens to antigen-presenting cells, particularly dendritic cells. This triggers an immune response by presenting these antigens to immune cells via the major histocompatibility complex classes I and II, activating the adaptive immune system.[3]

mRNA-based therapies include various strategies to alter the expression of disease-causing genes and proteins, where therapeutic vaccination is the most used mRNA based anti-cancer approach. mRNA-4157, Moderna's personalized cancer vaccine has advanced into late-stage development for melanoma based on promising Phase II results.[4] BioNTech is advancing its uridine mRNA-lipoplex (LPX) cancer vaccine portfolio with the FixVac and iNEST platforms to enhance vaccine efficacy and stability.[5] Gritstone bio's most advanced self-amplifying mRNA (samRNA) vaccine program GRANITE has shown preliminary encouraging results in combination with immune checkpoint inhibitors (ICI) for microsatellite-stable (MSS) colorectal cancer (CRC) patients.[6]

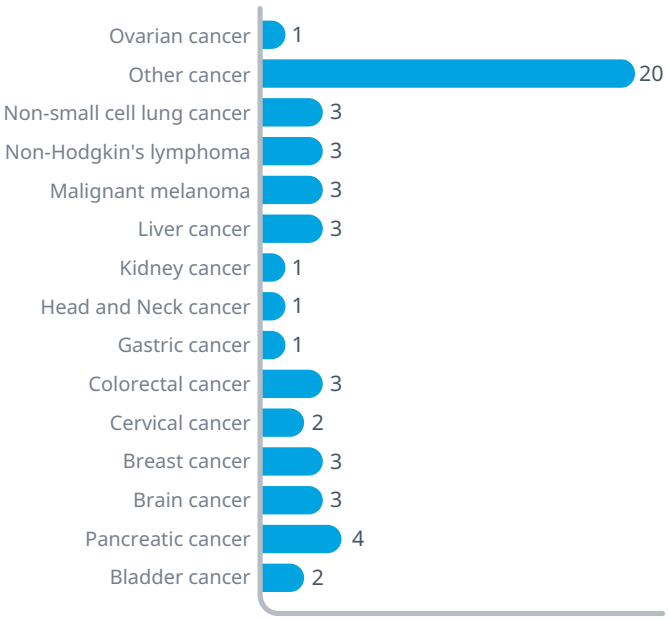
Another immunotherapeutic approach using mRNA-transfected CAR-T cells has entered clinical stage with Regeneron's mRNA CAR-T therapy bbT369 under Phase I/II (NCT05169489) evaluation for relapsed or refractory B cell non-Hodgkin's lymphoma.[7]

Immuno-epigenetic modulation, which utilizes mRNAs to deliver epigenetic regulators, such as cytokines, to silence oncogenes and activate the immune system, is also advancing as an innovative strategy in cancer treatment, with therapies like OTX-2002 and ABO2011 in early development stages.[8]

mRNA pipeline insights: Overview on tumor type, product type and target

As of October 2024, IQVIA's Pipeline Link/Trial Link listed a total of 36 mRNA-based oncology therapies developed either as monotherapy or in combination with other drugs across different tumor types in adults aged 18 years and above. The majority of drugs in development are for solid tumors followed by liquid tumors (illustrated in Figure 1). Trial Link recorded 51 clinical trials, including 34 currently recruiting participants. Many of these trials are in Phase I and Phase II, with ongoing efforts to optimize delivery systems and enhance efficacy and 2 programs are in late Phase II/III and Phase III stages.

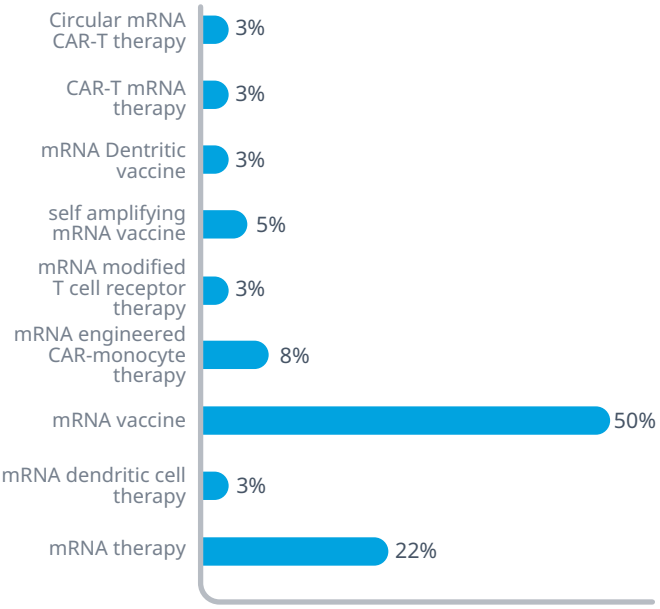
Figure 1: Tumor type wise distribution of mRNA assets in oncology



Source: IQVIA Pipeline Link/Trial Link.

mRNA-based therapies are transforming the landscape of cancer treatment by offering a range of approaches from vaccines to cell-based therapies, each with unique mechanisms to tackle different aspects of tumor biology. The mRNA therapy oncology pipeline is dominated by approximately 50% of mRNA vaccines (illustrated in Figure 2) due to their relatively straightforward production and broad applicability. Companies like Moderna, BioNTech, and CureVac are driving this field, with several vaccines in advanced stages of development. Additionally, mRNA therapies have gained interest by occupying 22% of ongoing Phase I and II trials by its unique direct administration to activate immune cells in the tumor microenvironment, followed by other types, including 14% CAR-mRNA therapies especially with the rise of engineered cell-based therapies. Dendritic cell therapies and mRNA modified T cell receptor therapies are also progressing, with promising results in early trials.

Figure 2: Molecule types in development for mRNA in oncology

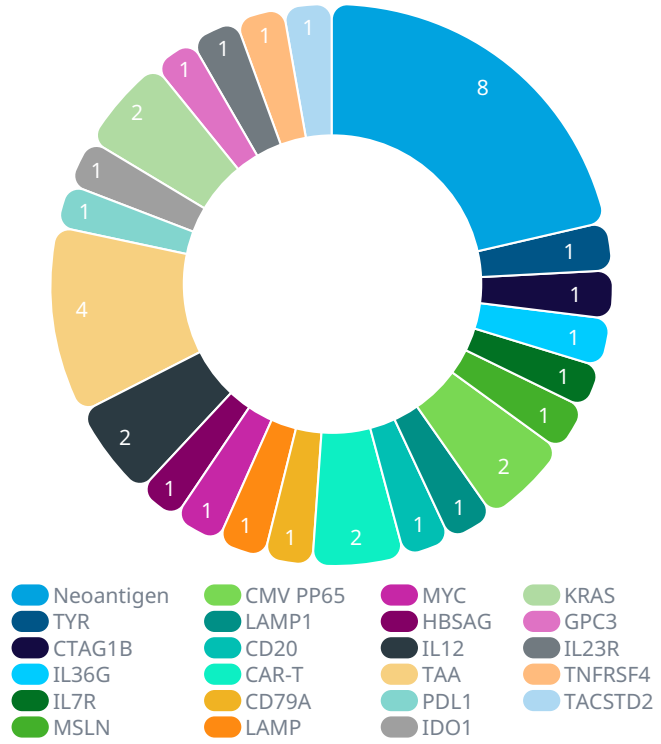


Source: IQVIA Pipeline Link/Trial Link.

mRNA therapies offer unique benefits over conventional therapies like recombinant proteins and plasmid DNA, including non-integrating, cell-free production, enhanced specificity, and potency, as well as a personalized, patient-focused approach.

According to IQVIA Pipeline Link and Trial Link, current analyses indicate that neoantigens are at the forefront of mRNA therapy research, with a substantial proportion of 8 clinical assets focusing on personalized neoantigen target (illustrated in Figure 3). Following neoantigens, TAA, KRAS and CMV pp65 are among the other frequently targeted antigens due to their prevalence in common cancers.

Figure 3: Targets in development for mRNA therapies in oncology



Source: IQVIA Pipeline Link/Trial Link.

In contrast, other targets overexpressed in various cancers such as LAMP1 with its ability to enhance the presentation of antigen to CD4+ T cells, and other clinically relevant targets involved in cancer cell growth and metastasis such as TYR, TACSTD2, CTAG1B represent emerging areas of interest with fewer ongoing trials but significant potential. Targets like CD20, IDO1, MYC and IL-12 are also frequently explored in clinical trials due to their role in cancer epigenetics, though less prevalent.

Gritstone bio's heterologous prime-boost Phase II/III GRANITE, a personalized neoantigen adenoviral vectors-based samRNA vaccine, tackles the issue of immune non-reactivity in solid tumors and has the potential to be effective in tumors that do not respond to anti-PD(L)-1 therapy. Interim data from the ongoing Phase II/III trial (NCT05141721) of this vaccine, in combination with ICIs in addition to fluoropyrimidine/bevacizumab, showed a 21% relative risk reduction of progression in the all-treated population and a 38% relative risk reduction of progression in the low circulating tumor DNA subgroup versus control group in frontline MSS-CRC patients where there is significant unmet need. The conventional chemotherapy is primarily palliative and has shown benefits in the mismatch repair-deficient population, which represents only approximately 5% of metastatic cases.[6] The product was granted Fast Track designation by the US FDA for the treatment of MSS-CRC in December 2018.[9] The company plans to report overall survival (OS) data in second half 2025 and will review the progression-free survival data with the US FDA in 2024 for the pivotal trial design.[6] According to IQVIA Pipeline Link, this product is expected to reach the market by Q2 2027.

Moderna is pioneering a new era of cancer vaccines with its Merck-partnered mRNA-4157/V940, an individualized neoantigen vaccine encoding up to 34 different patient-specific neoantigens, which is currently being evaluated in Phase III trials for different tumor types, including adjuvant melanoma (NCT05933577), adjuvant NSCLC (NCT06077760) and adjuvant/neoadjuvant cutaneous squamous cell carcinoma (NCT06295809). In a 3-year median follow-up analysis from the Phase IIb KEYNOTE-942/mRNA-4157-P201 trial (NCT03897881), mRNA-4157 in combination with pembrolizumab showed significant and durable improvement in recurrence-free survival (RFS) and distant metastasis-free survival compared with pembrolizumab alone in resected melanoma patients, reducing the risk of recurrence and distant metastasis by 49% and 62%, respectively. The 2.5-year RFS rate was 74.8% for the combination as compared to 55.6% for pembrolizumab alone.[10] The product gained Fast Track designation from the US FDA in 2022[11] and the company is planning regulatory discussions for the adjuvant melanoma program which is expected to be launched in the market by Q3 2030, according to IQVIA Pipeline Link.

BioNtech's BNT111 vaccine, is being evaluated in a Phase II trial (NCT04526899) in combination with the anti-PD-1 antibody cemiplimab for patients with unresectable stage III or stage IV melanoma who are refractory to or have relapsed after anti-PD-1 therapy. The data showed that the vaccine holds great potential as a treatment option for melanoma and may prove to be an alternative therapy in patients with advanced forms of the disease. The product has gained Fast Track Designation by the US FDA for the treatment of advanced melanoma in November 2021.[12]

Novel therapies in early-stage

BNT122/RG6180 (autogene cevumeran)

BioNTech in collaboration with Roche, is developing autogene cevumeran, a uridine mRNA- LPX individualized vaccine encoding up to twenty patient-specific neoantigens. It has shown a poly-epitopic neoantigen-specific T-cell response in patients with resected stage II/III CRC after completing adjuvant chemotherapy, resulting in all evaluated patients being disease-free at the data cut-off, as per the immunogenicity results from the biomarker cohort of the ongoing Phase II trial (NCT04486378), with preliminary data expected in late 2025 or 2026.[13] As per 3-year follow-up data from a Phase I trial (NCT04161755) in surgically resected pancreatic ductal adenocarcinoma (PDAC) patients, autogene cevumeran demonstrated prolonged RFS compared to non-responders and induced de novo 79 CD8+ T cell clones in the blood with an estimated median lifespan of 5.5 year, 98% of which were not present in pre-vaccination host tissues. It is now being evaluated in the Phase II IMCODE003 trial (NCT05968326) for adjuvant PDAC in combination with atezolizumab and mFOLFIRINOX.[14] Additionally, a Phase II trial for first-line advanced melanoma in combination with pembrolizumab (NCT03815058) is in progress.

OTX-2002

Omega Therapeutics' OTX-2002 is an epigenomic controller designed to target a specific EpiZip to downregulate MYC expression pre-transcriptionally, while preserving healthy cells and potentially bypassing autoregulation, and holds potential to effectively treat ICI-resistant or refractory tumors clinically. As per preliminary results from initial cohorts of the ongoing Phase I/II MYCHELANGELO trial (NCT05497453), OTX-2002, both as a monotherapy and in combination with standard of care, led to decreased MYC mRNA levels and specific epigenetic modifications in patients with challenging, heavily pretreated hepatocellular carcinoma (HCC), and other c-MYC associated solid tumors. The company is planning to select the recommended dose for expansion into monotherapy and combination settings and disclose updated clinical data from monotherapy dose escalation in Q4 2024.[15]

LIOCYX-M

Lion TCR is evaluating LioCyx-M, an autologous immunotherapeutic T cell product transiently modified with in-vitro transcribed mRNA encoding a hepatitis-B-virus (HBV)-specific T cell receptor, in a Phase I/II trial (NCT05195294) as a monotherapy and in combination with lenvatinib for advanced HBV-related HCC. It has shown specific targeting effect with activation of proliferative T cell factors and/or elevation of serum inflammatory chemokines CXCL9 and CXCL10 in a Phase I dose-escalation trial and median OS was 33.1 months as of January 2022.[16]

MT-302 and MT-303

Myeloid Therapeutics is advancing its monocyte-derived cell therapy portfolio which utilizes mRNA engineering to insert a chimeric antigen receptor into the patient's myeloid cells. MT-302, a TROP2-targeting mRNA-based CAR therapy, has shown preclinical safety and efficacy signals in patients with metastatic epithelial tumors, and is being assessed in the Phase I MYE Symphony trial (NCT05969041) for adult patients with advanced or metastatic epithelial tumors.[17] Another candidate MT-303, a Glypican-3 (GPC3) targeted mRNA CAR, has advanced into Phase I stage (NCT06478693) for adult patients with advanced or metastatic HCC with overexpressed GPC3 based on compelling activity in GPC3/HCC preclinical model eliciting strong expression in myeloid cells and had a satisfactory safety profile.[18]

mRNA therapies clinical trial landscape in oncology

As of October 2024, Trial Link listed 51 ongoing clinical trials, including 24 trials in Phase II and III development that are mentioned in Table 1 on the following page as per their highest phase in specific disease.

Collectively, preclinical, and clinical studies on mRNA-based cancer immunotherapies are rapidly evolving to enhance cancer patient care.

Table 1: List of ongoing clinical trials involving mRNA therapies for oncology

DRUG/ TARGET	COMPANY	HIGHEST PHASE	ROA/ PRODUCT TYPE	NCT ID (ENROLLMENT)	DISEASE	TRIAL START DATE	PRIMARY COMPLETION DATE	FIRST LAUNCH DATE*	NUMBER OF SITES (COUNTRIES)
mRNA-4157 vaccine/ neoantigen	Moderna/ Merck & Co	Phase III	VIAL (mRNA vaccine	NCT06295809 (1012)	OTHER CANCER	18/04/2024	30/04/2029	Q3 2030	70 (USA+17)
				NCT05933577 (1089)	MALIGNANT MELANOMA	19/07/2023	26/10/2029		161(USA+24)
				NCT06305767 (230)	BLADDER CANCER	28/03/2024	8/10/2026		61 (USA+14)
				NCT06077760 (868)	NON-SMALL CELL LUNG CANCER	6/12/2023	25/06/2030		135 (USA+27)
				NCT06307431 (272)	KIDNEY CANCER	10/4/2024	8/1/2028		47 (USA+11)
GRANITE (GRT-C901/ GRT-R902)vaccine, neoantigen	Gritstone Bio	Phase II/III	VIAL (Self-amplifying mRNA vaccine)	NCT05141721 (700)	COLORECTAL CANCER	12/2/2022	31/03/2027	Q2 2027	43 (USA)
BNT111 TYR, vaccine, CTAG1B	BioNTech	Phase II	VIAL (mRNA vaccine)	NCT04526899 (184)	MALIGNANT MELANOMA	19/05/2021	25/01/2024	Q4 2028	53 (USA+6)
OTX-2002 MYC	Omega Therapeutics	Phase I/II	VIAL (mRNA therapy)	NCT05497453 (190)	LIVER CANCER AND OTHER CANCER	19/08/2022	30/06/2025	Q4 2029	15 (USA+4)
BNT122 (autogene cevumeran) vaccine, neoantigen	BioNtech/ Roche	Phase II	VIAL (mRNA vaccine)	NCT03815058 (131)	MALIGNANT MELANOMA	8/1/2019	30/10/2025	Q2 2030	57 (USA+5)
				NCT04486378 (229)	COLORECTAL CANCER	8/3/2021	28/02/2026		113 (USA+5)
				NCT03289962 (272)	OTHER CANCER	21/12/2017	1/11/2024		37 (USA+7)
				NCT05968326 (260)	PANCREATIC CANCER	18/10/20230	27/12/2029		45 (USA+6)
				NCT06534983 (362)	BLADDER CANCER	31/07/2024	6/11/2028		7 (USA+4)
BNT116 vaccine, TAA	BioNTech	Phase II	VIAL (mRNA vaccine)	NCT05557591 (100)	NON-SMALL CELL LUNG CANCER	21/04/2023	2/3/2027	Q3 2031	55 (USA +6)
STX-001 IL12	Strand Therapeutics	Phase II	VIAL (mRNA therapy)	NCT06249048 (108)	OTHER CANCER	3/5/2024	31/05/2027	Q4 2031	4 (USA +1)
mRNA-4359 PDL1, IDO1, vaccine	Moderna	Phase I/II	VIAL (mRNA vaccine)	NCT05533697 (194)	OTHER CANCER	18/08/2022	8/12/2027	Q2 2032	26 (USA+3)
BNT113 vaccine	BioNTech	Phase II	VIAL (mRNA vaccine)	NCT04534205 (285)	HEAD & NECK CANCER	7/1/2021	31/05/2028	Q4 2032	168 (USA+21)
ITI-1000 (Umitrelimorgene autodencel) CMV PP65, LAMP1	Immunomic Therapeutics	Phase II	VIAL (mRNA dendritic cell therapy)	NCT02465268 (175)	BRAIN CANCER	9/8/2016	30/11/2023	Q2 2029	3 (USA)
LioCyx-M HBSAG	LION TCR	Phase I/II	VIAL (mRNA modified T cell receptor therapy)	NCT05195294 (55)	LIVER CANCER	30/06/2022	28/02/2026	Q3 2030	NA
bbT369 CD20, CAR-T, CD79A	Regeneron	Phase I/II	VIAL (CAR-T mRNA therapy)	NCT05169489 (50)	NON-HODGKIN's LYMPHOMA	24/01/2022	31/08/2024	Q2 2029	4 (USA)
RG002 vaccine	RinuaGene	Phase I/II	VIAL (mRNA vaccine)	NCT06273553 (39)	CERVICAL CANCER	31/03/2024	31/10/2026	Q2 2032	NA
CMV pp65-LAMP mRNA-pulsed DC Vaccine (CLDX) vaccine, CMV PP65, LAMP	Celldex	Phase II	VIAL (mRNA dendritic cell vaccine)	NCT03688178 (43)	BRAIN CANCER	26/08/2020	31/03/2025	Q3 2029	1 (USA)

* Source: IQVIA Pipeline Link

Conclusion and future perspectives

Decades of scientific and clinical research, along with considerable achievements in COVID-19 vaccines, augur well for the future of mRNA therapeutics. mRNA cancer vaccines are emerging as a viable option for personalized cancer treatment, as evident from early-stage clinical data of Gritstone's GRANITE and Moderna's mRNA-4157, which are expected to reach the market by Q2 2027 and Q3 2030 respectively, according to IQVIA Pipeline Link and Trial link. Moreover, combining mRNA therapies with other treatment regimens such as ICIs, chemotherapy, radiation therapy, has shown initial promise in enhancing therapeutic response and efficacy.

The field of programmable mRNA therapeutics is also on the horizon with Omega's Epigenomic Controller OTX-2002 reducing the expression of oncogene c-Myc, a historically 'undruggable' target and a key driver of cancer proliferation and immune evasion in over 50% of human cancers. Collectively, preclinical, and clinical studies on mRNA-based cancer immunotherapy are rapidly evolving to enhance cancer patient care. However, future focus is to fully utilize advanced therapeutic modality, which includes optimizing neoantigen-specific cancer vaccines, understanding the biology of immune escape in cancer, and balancing the anti-cancer immune response.[19]

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